of when a diagnostic test can safely be used to rule out tuberculous meningitis.

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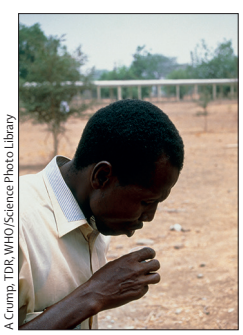
Performance of Xpert MTB/RIF Ultra: a matter of dead or alive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See Articles page 76

In our opinion, the implementation of the Xpert MTB/RIF assay (Cepheid, Sunnyvale, CA, USA) since 2010 has revolutionised molecular diagnosis of (multidrug-resistant) tuberculosis. Xpert combines early diagnosis of tuberculosis with direct detection of rifampicin resistance, but the limitations of the assay are its suboptimal sensitivity and high rate of false positivity in low-prevalence settings. To overcome these limitations, the assay was re-engineered to increase diagnostic sensitivity and improve specificity in the detection of rifampicin resistance. The resulting Xpert MTP/RIF Ultra (Xpert Ultra) assay is run on the same device as Xpert and requires only a software upgrade.[1] In *The Lancet Infectious Diseases*, Susan Dorman and colleagues[2] report the results of a comparison between Xpert Ultra with Xpert assay performance on sputum samples from 1753 patients tested at ten reference laboratories in eight tuberculosis high-endemic countries.

Xpert and Xpert Ultra had roughly similar performance in the detection of rifampicin resistance, but Xpert Ultra had a higher overall sensitivity than Xpert (88% [95% CI 85–91] with Xpert Ultra *vs* 83% [79–86] with Xpert)—the difference being more pronounced in smear-negative cases (63% [54–71] *vs* 46% [37–55]) and in HIV co-infected cases (90% [83–90] *vs* 77% [68–84]).[2] Xpert Ultra's improved sensitivity was, however, associated with a 2% lower specificity than Xpert (96% [94–97] *vs* 98% [97–99]). The specificity of Xpert Ultra for detection of *Mycobacterium tuberculosis* was even lower in patients with previous tuberculosis or from high-incidence countries.

The increased sensitivity and reduced specificity of Xpert Ultra compared with Xpert translates into a higher negative predictive value but a lower positive predictive value. These effects, which seem counterintuitive, are shown in the figure in terms of Bayes' theorem of conditional probabilities (figure). Compared with a useless test, a positive test result increases and a negative test result decreases the probability of tuberculosis, but to a different extent for Xpert and Xpert Ultra. In terms of percentage, the increase in sensitivity of Xpert Ultra exceeds the decrease in specificity.[2] However, the number of participants with culture-negative sputum (n=977) was twice that of

participants with culture-positive sputum (n=462). The observed percentages thus correspond to an additional 25 patients with positive-culture sputum diagnosed early by Xpert Ultra but not by Xpert, at a cost of 26 additional false-positive Xpert Ultra results that were culture-negative.

We assume the observed excess of false-positive Xpert Ultra results can be explained by detection of DNA from non-viable *M tuberculosis*, a phenomenon previously shown for Xpert.[3] The origin of *M tuberculosis* DNA in sputum in the absence of viable bacilli could be residual tuberculosis lesions after treatment, as prolonged excretion of *M tuberculosis* DNA has been demonstrated.[4] Perhaps we should view tuberculosis as a spectrum of diseases,[5,6] with subclinical, self-contained tuberculosis or even a stage of latent tuberculosis as other possible sources of *M tuberculosis* DNA in sputum.

In the study by Dorman and colleagues,[2] positive results due to DNA from dead bacilli are only named false positive because the gold standard was culture. Although both Xpert and Xpert Ultra are designed to detect *M tuberculosis* DNA, dead or alive, the clinical question is whether viable *M tuberculosis* is present. Thus, the tests answer a different question. By contrast, a study by Bahr and colleagues[7] compared Xpert Ultra with Xpert for detection of *M tuberculosis* in cerebrospinal fluid, showing that Xpert Ultra's sensitivity was superior even compared with culture. The specificity of both tests was very high and comparable because the gold standard was a clinical case definition, and detection of *M tuberculosis* DNA was always considered significant. We show the unambiguous advantages of Xpert Ultra (figure), which was named a possible game changer in that setting.[8]

The ultimate cause of detection of DNA from dead bacilli is its high stability, which is just what palaeomicrobiology makes use of; *M tuberculosis* DNA has even been detected in millennia-old human remains.[9] Interestingly, the target region for such studies was IS*6110*, one of the two multicopy sequences for which additional primers were included in Xpert Ultra.[1] A test that exclusively identifies viable *M tuberculosis* would be the solution, for example by detection of *M tuberculosis* mRNA or analysis of exhaled breath for organic volatile compounds of *M tuberculosis*.[4,10] However, these methods never passed the research stage of development.

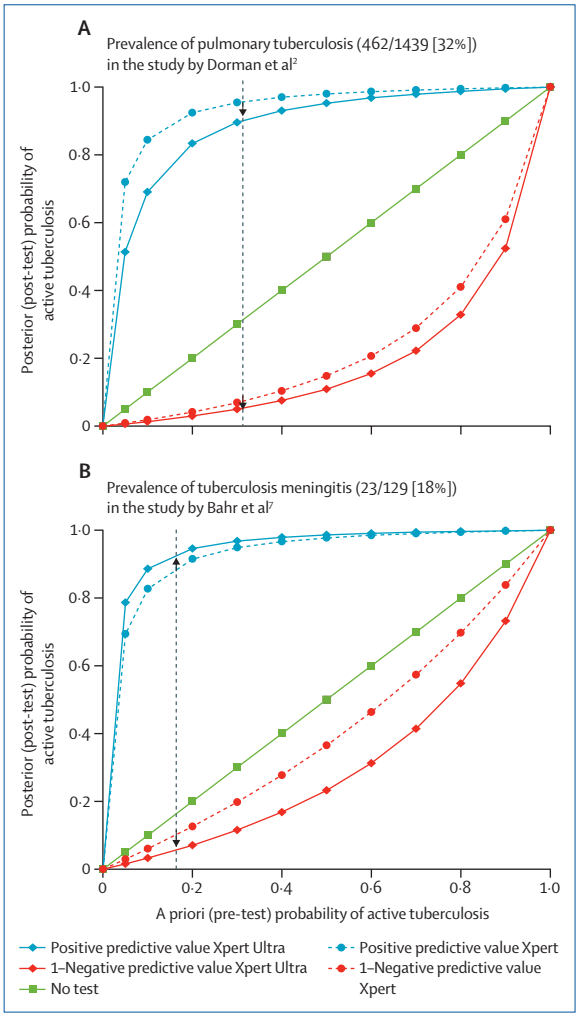

***Figure*: Post-test probability of tuberculosis based on the sensitivity and specificity of Xpert MTB/RIF and Xpert MTB/RIF Ultra (Xpert Ultra) assays, as observed in two recent studies[2,7]**

(A) Constructed using Xpert and Xpert Ultra sensitivity (0·83 *vs* 0·88) and specificity (0·98 *vs* 0·96) on sputum samples, as observed in the study by Dorman and colleagues.[2] (B) Constructed using the sensitivity of Xpert (0·43) and Xpert Ultra (0·70) on cerebrospinal fluid, as observed in the study by Bahr and colleagues.[7] The specificity is arbitrarily set at 0·99 with the assumption that false-positive results in cerebrospinal fluid are highly unlikely, as explained by Bahr and colleagues.[7] The green lines indicate the post-test probability of tuberculosis using a test without diagnostic value, which equals the pre-test probability (x=y). The blue lines indicate the positive predictive value of Xpert (dashed line) and Xpert Ultra (continuous line), which is the proportion of true positive results. The red lines indicate the proportion of false-negative results for Xpert (dashed line) and Xpert Ultra (continuous line), which equals 1 minus the negative predictive value. The vertical dashed lines in each panel indicate the prevalence of tuberculosis in each study. The arrows between the blue lines indicate the change of the positive predictive value if Xpert Ultra replaces Xpert (decrease in panel A and increase in panel B). The arrows between the red lines indicate the change in the rate of false-negative results if Xpert Ultra replaces Xpert (decrease in both panels). The Bayes graph creator can be used to compare any two tests for which the sensitivity and specificity are known (appendix).

See **Online** for appendix

Based on a technical expert consultation, WHO states that Xpert Ultra can replace Xpert in all settings.[11] However, such replacement comes with pros, cons,

and unknowns.[12] Metaphorically speaking, if Xpert is a knife, Xpert Ultra is a sharper knife. However, the trade-off of the higher sensitivity is a lower specificity, as is customary for diagnostic tests. We eagerly await additional studies and algorithms that assess Xpert Ultra's improved sensitivity and solutions to avoid the trap of treating patients for dead bacilli.

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Pre-exposure prophylaxis is cost-effective for HIV in the UK

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See **Articles** page 85

At the International AIDS Society (IAS) conference in Paris, France, in July, 2017, new data were presented showing a large reduction in HIV diagnoses in the UK's largest sexual health clinic. 56 Dean Street in Soho (London, UK) saw a 42% drop in new diagnoses between 2015 and 2016.[1,2] Similarly promising findings were reported in studies of clinics in France and Australia. This reduction is likely to be due to increased testing, earlier diagnosis, and immediate initiation onto HIV treatment at diagnosis,[3] as well as increased availability of pre-exposure prophylaxis (PrEP) for HIV.

In *The Lancet Infectious Diseases*, Valentina Cambiano and colleagues[4] directly address a key issue of PrEP: the cost-effectiveness of including it as part of the package of routine HIV care throughout the UK. The question is, given its budget impact, are the benefits of providing PrEP for men who have sex with men (MSM) likely to be greater or lower than the benefits associated with other health-care interventions, which will consequentially be forgone as a result of resources being committed to PrEP?

HIV incidence has been persistently high for years, particularly among MSM who, despite constituting a small percentage of the UK population, account for more than half of new HIV infections.[5] The PROUD[6] and IPERGAY[7] trials have shown the high levels of effectiveness of PrEP in reducing HIV infections among MSM, providing compelling evidence for its clinical effectiveness.

By contrast with the optimism surrounding the clinical effectiveness of PrEP, however, the current mood around funding and provision of sexual health services in the UK is bleak. NHS England (which funds HIV treatment) had initially refused to pay for PrEP, arguing that responsibility for HIV prevention services laid with local authorities. Following a judicial review and subsequent rejection of that decision, NHS England announced it would provide PrEP to 10 000 patients, but only through a large implementation study in selected clinics from September, 2017.[8] Presented as a means to identify optimal ways of delivery, this decision has been viewed by many as simply a strategy to postpone access across the country.

Cambiano and colleagues[4] deliver, to our knowledge, the most comprehensive PrEP modelling study ever done for the UK. The model is impressively calibrated to a wide range of data, reflecting what is currently known about patterns of